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Applicants : Martin FUHRMANN et al.

Art Unit: 1623

Serial No. : 10/785,013

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Title : METHOD FOR PREPARING A MIXTURE THAT CAN BE
GRANULATED AND CARNITINE-MAGNESIUM-
HYDROXYCITRATE

DECLARATION

Martin Fuhrmann declares and states:

- (1) He is a joint inventor of the invention disclosed in the above-identified application.
- (2) The following experiments were conducted by him or under his direct supervision.

Experiment 1

Preparation of L-carnitine-magnesium citrate

128 g of anhydrous citric acid and 39 g of Mg(OH)₂ pharm. are mixed in a kneader for small batches (HKD-T 0.6 IKA) with 36 g of deionized water (water content based on complete mixture: 11.6%) while heating to 73 °C for 40 min. 107.5 g of L-carnitine are then added thereto and kneading is continued at 49 to 50 rpm for 35 min. until a gummy white consistency results. After drying in vacuo at 90 °C for 4 h, the composition is dry and hard. The product is checked by IR and polarimetry and is very pure. The product dissolves in water without residue. The water content of the dried substance is 10.1 percent by weight.

Experiment 2

Preparation of L-carnitine-magnesium citrate

134 g of anhydrous citric acid and 38.5 g of Mg(OH)₂ pharm. are initially mixed in a centrifugal force mill for 7 min. and then mixed together with 36 g of deionized water (water content based on complete mixture: 11.4%) in a kneader for small batches (HKD-T 0.6 IKA) while heating to 79 °C for 30 min. 107.5 g of L-carnitine are then added thereto, and kneading is continued at 40 to 50 rpm for 45 min. until homogeneous. After drying in vacuo at 90 °C for 4 h, the composition is dry and hard. The product is checked for purity by IR and polarimetry and gives a clear solution in water. The water content of the dried substance is 8.8% by weight.

Experiment 3

Hygroscopicity test

The product mixtures from Experiments 1 and 2 granulated to a particle size of < 0.8 mm using a FREEWIT screening granulator are stored at a relative humidity of 56 percent at 25 °C under constant test conditions for the stated times. The sample was previously dried to constant weight over phosphorus pentoxide. The moisture uptake from the air is determined by gravimetry. The weight gain is stated in percent based on the total weight of the sample. Conventional L-carnitine-magnesium citrate from the production method of European Published Patent Application 402,755 (U.S. Patent No. 5,071,874), which has been press-granulated to the same particle size, serves as the

reference sample and is comparable in terms of the particle properties (flow, low dust).

Storage time/h	+% by weight reference	+% by weight Experiment 1	+% by weight Experiment 2
4	5.1	2.0	2.7
8	9.1	2.2	3.0
24	18.1	4.6	5.4
36	17.6	4.4	5.5
48	20.4	5.2	6.4
336	15.6	5.1	6.5

Experiment 4

Preparation of L-carnitine-magnesium (-)-hydroxycitrate

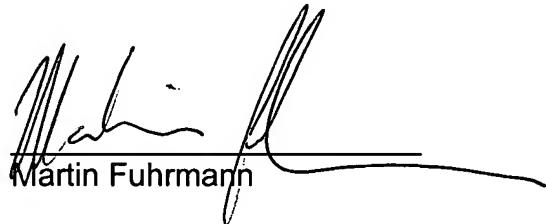
Preparation takes place in the method described in Experiment 2, mixing 83 g of carnitine (free base), 137 g of (-)-hydroxycitric acid HCA-650 77.7 percent, 30 g of Mg hydroxide and 55 g of water. The weight gain of the mixture of the invention, which had previously been dried was, after 24 h under standard conditions, 0.82 percent by weight. At a relative humidity of 56 percent, the water uptake of the mixture determined by gravimetry was ≤ 10 percent by weight after 30 h, corresponding to about 30 percent by weight based on the carnitine content of the mixture.

(3) L-carnitine, magnesium hydroxide and citric acid are mixed in stoichiometric amounts, i.e., in a molar ratio of approximately 1:1:1, to prepare a salt thereof. The types of these substances are preferably sufficiently pure, i.e., approved for the manufacture of food products or the preparation of pharmaceuticals, as are described, for example, in the European Pharmacopoeia. Anhydrous types are expediently used. To avoid an unwanted

salt loading, the pure L-carnitine is preferably added to the mixture as neutral inert salt. Compared with previous methods of preparation, the hygroscopicity of the complex salt L-carnitine-magnesium citrate prepared in this way is reduced further. For example, the moisture uptake, determined by gravimetry in the way familiar to the skilled worker, of solid carnitine-Mg citrate prepared by the method of the invention and previously dried to constant weight under oil-pump vacuum or over phosphorus pentoxide is not more than 7 percent by weight after 48 h at 56 percent relative humidity (rH). This figure is not exceeded even after storage for 330 h. Based on the amount of carnitine or carnitine derivative present in the mixture, referred to within the scope of the invention as carnitine content based on free base, this corresponds to a moisture uptake of not more than 40 percent by weight.

April 11, 2006

Date


Martin Fuhrmann